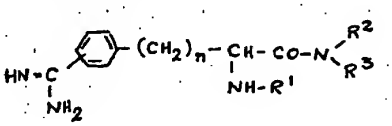
(12) UK Patent Application (19) GB (11) 2 007 663 A

(21) Application No 7843320
(22) Date of filing 6 Nov 1978
(23) Claims filed 6 Nov 1978
(30) Priority data
(31) 201898
(32) 7 Nov 1977
(33) Dem. Rep. of Germany (DD)
(43) Application published 23 May 1979
(51) INT CL²
C07C 143/80 A61K 31/18 31/40 31/445 31/535 C07D 295/18
(52) Domestic classification
C2C 1341 1414 1532 1562 215 21X 220 222 226 227 22Y 250 251 252 255 25Y 280 282 292 29X 29Y 305 30Y 313 314 316 31Y 320 321 326 328 32Y 338 339 342 34Y 351 352 355 364 366 367 368 36Y 373 37Y 380 385 386 402 40Y 440 45X 45Y 490 510 51X 534 535 573 591 620 628 62X 635 638 650 652 658 65X 699 761 764 802 80Y KK KN LR SG SJ TL
(56) Documents cited
None
(58) Field of search
C2C
(71) Applicants
VEB Arzneimittelwerk Dresden, 35 Wilhelm-Pieck-Strasse, 8122 Radebeul, German Democratic Republic, GDR
(72) Inventors
Günther Wagner, Peter Richter, Heidemarie Horn, Bernd Voigt, Fritz Markwardt, Peter Walsmann
(74) Agents
Venner, Shipley & Co

(54) Sulphonylated ω-amidinophenyl-α-aminocarboxylic acid amides

(57) Compounds of the general formula:—



wherein R^1 is an alkylsulphonyl radical containing up to 6 carbon atoms or an arylsulphonyl radical containing 6 to 10 carbon atoms, R^2 is a hydrogen atom, an alkyl radical containing up to 8 carbon atoms, an aryl radical containing 6 to 10 carbon atoms or an aralkyl radical containing up to 3 carbon atoms in the side chain, R^3 is an alkyl radical containing up to 8 carbon atoms, an aryl radical containing 6 to 10 carbon atoms or an aralkyl radical containing up to 3 carbon atoms in the side chain, or R^2 and R^3, together with the nitrogen atom to which they are attached, can also form a 5- to 7-membered heterocyclic ring which can contain one or more further heteroatoms and/or can be substituted and *n* is 0, 1, 2 or 3; as well as the acid-addition salts thereof with physiologically acceptable inorganic and organic acids have anticoagulant activity.

GB 2 007 663 A

SPECIFICATION

Sulphonylated ω-amidinophenyl-α-amino Carboxylic Acid Amides, the Preparation Thereof and Pharmaceutical C mpositions Containing them

The present invention is concerned with N_α-alkyl- and N_α-arylsulphonylated ω-amidinophenyl-α-amino-alkylcarboxylic acid amides and with the preparation thereof.

The new compounds according to the present invention are thrombin inhibitors and can, therefore, be advantageously used directly as anticoagulants.

For the therapy and prophylaxis of thrombotic diseases, in medical practice there have hitherto been used direct and indirect anticoagulants of the heparin type, as well as coumarin and indandione derivatives. However, both types of anticoagulants suffer from certain disadvantages. The action of the coumarin derivatives is directed towards the biosynthesis of the vitamin K-dependent coagulation factors II, VII, IX and X and their effect, which results in a reduction of the coagulation potential in the patient's blood, only manifests itself some time after administration. Therefore, the therapy requires laboratory monitoring since, in case of overdosage, haemorrhages can result.

Heparin, which because of its polysaccharide structure can only be administered parenterally, acts as a catalyst in the body's inactivation mechanism. Due to its polyvalent affinity, its action can be neutralised or weakened by reaction with other components of the blood, such as lipoproteids, platelet factor IV and the like. Its action is dependent upon a normally functioning antithrombin level in the blood.

Small molecule enzyme inhibitors have, in comparison with heparin, the advantage that they act directly and can also be administered orally. Their action takes place only after activation of the normally inactive zymogen prothrombin to give the active enzyme thrombin. For the action of such inhibitors, no other blood components are necessary; such as antithrombin for the action of heparin. In comparison with anticoagulants of the coumarin type, they have the particular advantage of manifesting their action immediately after administration.

The previously known enzyme inhibitors derived from benzamidine, for example *p*-amidinophenylpyruvic acid (see Richter and Wagner, German Democratic Republic Patent No. 87029 and Pharmazie, *28*, 514 and 585/1973) display a polyvalent inhibitory action against serine proteinases (see Markwardt *et al.*, German Democratic Republic Patent No. 92302). Besides thrombin, they also inhibit, *inter alia*, trypsin, plasmin, Factor Xa and serum kallikrein with a considerable degree of activity (see Geratz, Arch. Biochem. Biophys., *118*, 90/1967; Geratz, Experientia, *25*, 483/1969; Geratz, Amer. J. Physiol., *216*, 1812/1969; Markwardt *et al.*, European J. Biochem., *6*, 502/1968; Markwardt *et al.*, Experientia, *24*, 25/1968; Markwardt *et a.*, Acta biol. med. germ., *24*, 401/1970; Sturzbecher *et al.*, Thrombos. Res., *9* 637/1976).

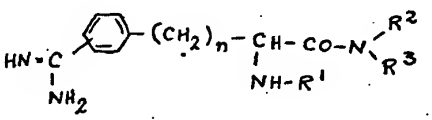
In the case of other enzyme inhibitors derived from benzamidine, for example, bis-(amidinobenzylidene)-cycloalkanones and bis-(amidinobenzyl)-cycloalkanones (see Wagner *et al.*, Pharmazie, *32*, 141/1977), the toxicity is so great that they are unsuitable for use *in vivo* (see Walsmann *et al.*, Acta biol. med. germ., *35* Kl/1976; Hauptmann *et al.*, Acta biol. med. germ., *35*, 635/1976).

Substantially thrombin-specific inhibitors of the N_α-arylsulphonylarginine ester and amide types, especially the corresponding dansyl derivatives, have been found by Okamoto *et al.* (see Federal Republic of Germany Patent No. 2,438,851 and Japanese Patents Nos. 76 125 259; 76 125 262 and 76 131 864; Okamoto *et al.*, Kobe J. Med. Sci., *21*, 43/1973; Hijikata *et al.*, Thromb. Res., Suppl. II, *8*, 83/1976; Okamoto *et al.*, Thromb. Res., Suppl. II, *8*, 77/1976). A disadvantage in the preparation of these compounds is that, as a rule, the guanidine grouping of the arginine must be blocked with protective groups which are difficult to remove before further reactions can be carried out on the arginine. Furthermore, in the case of the dansyl derivatives, the isolation of pure reaction products gives rise to comparatively great difficulties.

It is an object of the present invention to overcome the disadvantages of these previously known anticoagulants of the heparin type, of coumarin, of indandione and of all their derivatives, of previously known small molecular enzyme inhibitors derived from benzamidine, as well as of the N_α-arylsulphonylarginine esters and amides. A further object of the present invention is to achieve a decisive advance in the production and use of thrombin inhibitors.

The problem forming the basis of the present invention is to provide thrombin inhibitors which are as specific as possible. Furthermore, processes are to be provided which permit the preparation of such inhibitors in a technically comparatively simple manner.

Thus, according to the present invention, there are provided compounds of the general formula:—

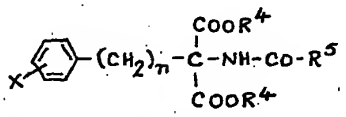


(I)

wherein R^1 is an alkylsulphonyl radical containing up to 6 carbon atoms or an arylsulphonyl radical containing 6 to 10 carbon atoms, R^2 is a hydrogen atom, an alkyl radical containing up to 8 carbon atoms, an aryl radical containing 6 to 10 carbon atoms or an aralkyl radical containing up to 3 carbon atoms in the side chain, R^3 is an alkyl radical containing up to 8 carbon atoms, an aryl radical containing 6 to 10 carbon atoms or an aralkyl radical containing up to 3 carbon atoms in the side chain, or R^2 and R^3, together with the nitrogen atom to which they are attached, can also form a 5- to 7-membered heterocyclic ring which can contain one or more further heteroatoms and/or can also be substituted, n, is 0, 1, 2 or 3 and the amidino radical can be in the m- or p-position; as well as the acid-addition salts thereof with physiologically acceptable inorganic and organic acids.

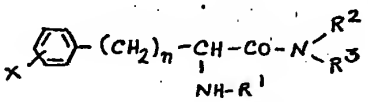
There are several different methods which can be used for the preparation of the new compounds (I), some of which are described in the following.

In the first place, an appropriate halophenylalkyl halide is reacted with an appropriate acylaminomalonic acid ester to give an ω-(halophenyl)-alkylacylaminomalonic acid diester of the general formula:—



(II)

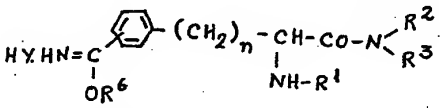
wherein n has the same meaning as above, R^4 and R^5, which can be the same or different, are alkyl radicals and X is a halogen atom. The compound thus obtained is reacted with a mixture of equal parts of 6N hydrochloric acid and glacial acetic acid under reflux conditions to give an ω-(halophenyl)-α-aminoalkyl-carboxylic acid hydrochloride which, by acylation with an appropriate sulphonic acid chloride in the presence of a base, is converted into the corresponding N_α-alkyl-sulphonyl or N_α-arylsulphonyl compound. The compound thus obtained is converted into the corresponding acid chloride, from which is obtained the corresponding acid amide of the general formula:—



(III)

wherein n, X, R^1, R^2 and R^3 have the same meanings as above.

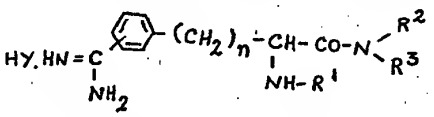
In the next step of the synthesis, the halogen atom attached to the aromatic nucleus is replaced by a cyano group by reaction with cuprous cyanide in dimethyl formamide in the presence of pyridine. The cyano compound thus obtained is converted with an anhydrous lower alcohol, as well as an anhydrous hydrogen halide, into an imide acid ester salt of the general formula:—



(IV)

wherein n, R^1, R^2 and R^3 have the same meanings as above, R^6 is an alkyl radical and Y is a halogen atom. The acid concentration is thereby to be kept low in order substantially to suppress the alcoholysis of the acid amide bond.

In the following synthesis step, by the action of ammonia in alcoholic solution on the imide acid ester salt, there is obtained the desired end product in the form of an amidine salt of the general formula:—



(V)

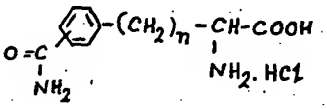
wherein n, Y, R^1, R^2 and R^3 have the same meanings as above.

Other amidine salts with physiologically acceptable inorganic or organic acids can be obtained by converting the imidoester hydrohalides into the imido ester bases, which are, in turn, converted into other imidoester salts which are then reacted in the above-described manner to give the corresponding amidine salts.

Furthermore, amidine salts can be obtained by reacting the imido ester bases with the ammonium salts of physiologically acceptable inorganic or organic acids to give the corresponding amidine salts.

A third possibility is to liberate the amidine base from the amidine salts and to react the free base with physiologically acceptable inorganic or organic acids to give other amidine salts.

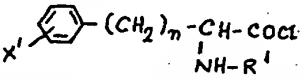
According to a second process, an appropriate cyanophenylalkyl halide is reacted to give an ω-(cyanophenyl)-acylaminomalonic acid diester. The compound thus obtained is dissolved, with warming, in a mixture of equal parts of glacial acetic acid and 6N hydrochloric acid and heated under reflux. There is thus obtained an ω-(carboxamidophenyl)-α-aminoalkyl-carboxylic acid hydrochloride of the general formula:—



(VI)

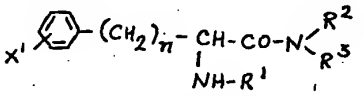
wherein *n* has the same meaning as above, which, by acylation with an appropriate sulphonic acid chloride in the presence of a base, is converted into a corresponding N_α-alkylsulphonyl- or N_α-arylsulphonyl compound.

The compound thus obtained is reacted with a small excess of thionyl chloride to give a mixture of a cyano compound (X′=CN) and an acid amide (X′=$CONH_2$) of the following general formula:—



(VII)

wherein *n* and R^1 have the same meanings as above. By reaction thereof with an appropriate amine in anhydrous benzene, there is obtained a mixture of compounds, in which X′ is CN or $CONH_2$, of the general formula:—

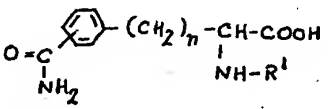


(VIII)

wherein *n*, R^1, R^2 and R^3 have the same meanings as above.

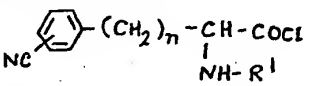
The pure cyano compound is obtained from this mixture with the use of phosphorus oxychloride in dimethylformamide (see El-Kerdasy *et al.*, Acta Pharm. Jugoslav., *26*, 141/1976).

In the case of this second process, it is especially advantageous to treat the carboxamido compound of the general formula:—



(IX)

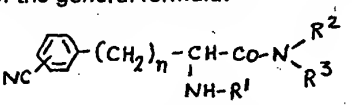
wherein *n* and R^1 have the same meanings as above, with an excess of an inorganic acid chloride, for example thionyl chloride (see Thurman, Chem. and Ind., *1964*, 752) so that, in addition to acid chloride formation, a quantitative dehydration of the primary acid amide groups also takes place, with the formation of a cyano compound of the general formula:—



(X)

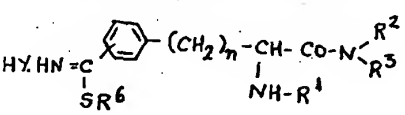
wherein *n* and R^1 have the same meanings as above. This acid chloride is, without isolation, directly converted into the corresponding acid amide which is reacted, in the manner described in the first process, *via* the imide acid ester salt, to give an amidine salt of general formula (V).

According to a third process, from an appropriate phenylalkyl halide substituted in the aromatic nucleus by a halogen atom or a cyano group, there is first prepared, in the manner described above in the first two processes, the corresponding ω-(cyanophenyl)-N_α-alkyl- or N_α-arylsulphonyl-α-aminoalkylcarboxylic acid amide of the general formula:—



(XI)

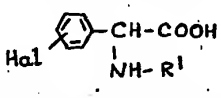
wherein *n*, R^1, R^2 and R^3 have the same meanings as above, to which hydrogen sulphide is added in triethylamine/pyridine to give the corresponding thiocarboxamide compound, which is then reacted with an appropriate alkyl halide to give a thioimide acid ester salt of the general formula:—



(XII)

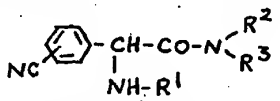
wherein *n*, Y, R^1, R^2 and R^3 have the same meanings as above and R^6 is an alkyl radical, which is reacted with ammonium acetate to give an amidine salt (V) (see Baker *et al.*, J. med. Chem., *10*, 1123/1967).

According to a fourth process, an appropriate halophenylglycine is N_α-alkylsulphonated or N_α-aryl-sulphonated to give a compound of the general formula:—



(XIII)

wherein Hal is a halogen atom and R^1 has the same meaning as above. The compound thus obtained is reacted with an inorganic acid chloride, for example thionyl chloride, to give the corresponding acid chloride which is then reacted to give the corresponding acid amide. Subsequently, this compound is heated under reflux with cuprous cyanide in an organic solvent, for example dimethylformamide, in the presence of an organic base, for example pyridine. After a reaction period of about 30 hours, there is obtained a product of the general formula:—



wherein R^1, R^2 and R^3 have the same meanings as above. The cyano compound obtained in the above-described manner is reacted, for example according to the reaction route given above in the third process, *via* the thiocarboxamido compound and subsequently *via* the thioimide acid ester salt, to give an N_α-alkyl- or N_α-arylsulphonyl-ω-amidinophenyl-α-aminoalkylcarboxylic acid amide (*I*). If desired, further reaction to give another salt with a physiologically acceptable inorganic or organic acid can be carried out in the manner described above in the case of the first process.

In the above-described processes, it is preferable to add the cuprous cyanide in several portions after reaction periods of about 8 hours. It is also advantageous to work under an inert gas atmosphere.

The present invention also provides pharmaceutical compositions containing at least one of the new compounds according to the present invention, in admixture with a solid or liquid pharmaceutical diluent or carrier. Examples of suitable forms of administration include tablets, dragees, capsules, suppositories, solutions and the like.

The following Examples are given for the purpose of illustrating the present invention:—

Example 1

6.5 g. 4-Bromobenzyl bromide are reacted in 25 ml. anhydrous dioxan with 5.7 g. diethyl acetaminomalonate, 0.3 g. potassium iodide and a sodium ethylate solution prepared from 0.65 g. sodium and 15 ml. anhydrous ethanol. For working up, the suspension obtained is reacted with a copious amount of water and the product, after crystallisation, is filtered off with suction, washed with water and recrystallised from methanol to give diethyl 4-bromobenzyl-acetaminomalonate; m.p. 131—133°C.; sublimes above 115°C.

7.0 g. Diethyl 4-bromobenzylacetaminomalonate are dissolved, with warming, in 35 ml. glacial acetic acid and the solution, after the addition of 35 ml. 6N hydrochloric acid, is heated under reflux for 6 hours. After cooling, the reaction product crystallises out. It is filtered off with suction and dried. If necessary, it can be purified by dissolving in methanol and reprecipitating by the addition of diethyl ether to give 4-bromophenylalanine hydrochloride; m.p. above 216°C.

5.6 g. 4-Bromophenylalanine hydrochloride are dissolved in 60 ml. 1N aqueous sodium hydroxide solution and shaken with a solution of 4.0 g. tosyl chloride in 20 ml. diethyl ether for 6 to 8 hours at ambient temperature. After separation of the ethereal phase, the aqueous solution is acidified with 6N hydrochloric acid and extracted with chloroform. Upon washing the chloroform solution with water, a part of the product already precipitates out. It is filtered off with suction. The part obtained after concentration of the dried chloroform solution is combined with the first part obtained and recrystallized from methanol to give N_α-tosyl-4-bromphenylalanine; m.p. 185—188°C., drops from 179°C.

6.3 g. N_α-Tosyl-4-bromophenylalanine are covered with 20 ml. thionyl chloride and the reaction mixture is heated for 45 minutes on a boiling water-bath. Excess thionyl chloride is then distilled off and the residue obtained is codistilled twice with about 25 ml. amounts of anhydrous benzene, the acid chloride remaining behind as a solid, yellowish residue. This is dissolved in anhydrous benzene and, while stirring, added dropwise to a solution of 3.0 g. piperidine in 20 ml. anhydrous benzene which has been cooled to 0 to 5°C. When the addition is complete, the reaction mixture is further stirred for 1 hour at ambient temperature. Subsequently, it is shaken up twice with water, N_α-tosyl-4-bromophenyl-alanine piperidide already beginning to crystallise out of the benzene phase. It is filtered off with suction, dried and, prior to recrystallisation, combined with the fraction obtained from the benzene solution after distilling off the solvent to give N_α-tosyl-4-bromo-phenylalanine piperidide; m.p. 181—183°C.

3.5 g. N_α-Tosyl-4-bromophenylalanine piperidide are dissolved in 27 ml. dimethylformamide, with the addition of 8 drops of anhydrous pyridine. After the addition of 0.81 g. cuprous cyanide, the solution is heated under reflux for 16 hours. After cooling, it is poured into a mixture of about 30 g. ice and 30 ml. 25% aqueous ammonia solution and left to stand for 15 hours at ambient temperature. Subsequently, the suspension obtained is stirred for 30 minutes with 50 ml. chloroform. The chloroform phase is then separated off, washed with water and dilute hydrochloric acid and, after washing until neutral, dried over anhydrous sodium sulphate. The residue obtained after distilling off the solvent is recrystallized from ethanol to give N_α-tosyl-4-cyanophenylalanine piperidine; m.p. 221°C.

0.41 g. of this cyano compound is dissolved, with warming, in 8 ml. anhydrous dioxan. After the addition of 0.3 g. anhydrous methanol, the solution is cooled to 0 to 5°C. and 0.5 g. dry hydrogen chloride gas passed in. The reaction mixture is left to stand for 3 days at ambient temperature. Subsequently, the imide acid ester salt is precipitated out by the addition of a copious amount of diethyl ether, left to crystallise and then filtered off with suction and taken up in methanol. After mixing the solution with a methanolic solution of ammonia, it is heated for 3 hours at 70 to 80°C. For working up, the solution is evaporated to dryness in a vacuum and the residue obtained taken up in a little methanol. The crystallisation which commences after a short time is completed by keeping for 15 hours at 0 to 5°C. The mother liquor is mixed with diethyl ether until a strong turbidity is obtained and the product, after crystallisation, is filtered off with suction. For purification, the compound is again dissolved in methanol, by products are separated off as a first fraction by the addition of a little diethyl ether and N_α-tosyl-4-amidinophenylalanine piperidide hydrochloride, after filtration, is precipitated out with diethyl ether. Thereafter it is again dissolved in methanol and reprecipitated with diethyl ether; m.p. 151—152°C.

Example 2

9.8 g. 4-Cyanobenzyl bromide are reacted in 50 ml. anhydrous dioxan with 10.9 g. diethylacetamidomalonate, 0.5 g. potassium iodide and a sodium ethylate solution prepared from 1.2 g. sodium and 20 ml. anhydrous ethanol. For working up, the suspension is mixed with a copious amount of water and the product, after crystallisation, filtered off with suction and recrystallised from methanol to give diethyl 4-cyanobenzyl-acetaminomalonate; m.p. 168—170°C.

7.6 g. Diethyl 4-cyanobenzylacetaminomalonate are dissolved, with warming, in a mixture of 15 ml. glacial acetic acid and 15 ml. 6N hydrochloric acid and the solution is heated under reflux for 3 hours. The part of the reaction product which crystallises out upon cooling is filtered off with suction and the filtrate is evaporated to dryness in a vacuum, finally while heating on a boiling water-bath. The residue which remains behind is taken up in methanol and the filtered solution mixed with diethyl ether until it is very turbid. The compound which crystallises out is filtered off with suction dried and combined with the first fraction to give 4-aminocarbonylphenylalanine hydrochloride; m.p. above about 200°C. (decomp).

4.5 g. 4-Aminocarbonylphenylalanine hydrochloride are dissolved in 55 ml. 1N aqueous potassium hydroxide solution and shaken with a solution of 3.6 g. tosyl chloride in 40 ml. diethyl ether for 7 hours at ambient temperature. Thereafter, precipitated potassium salt is filtered off with suction and the ethereal phase of the filtrate is separated off. The aqueous solution is shaken out twice with a little diethyl ether and acidified. The precipitate is, together with the fraction liberated from the potassium salt by treatment with dilute hydrochloric acid, filtered off with suction, washed with water and dried. For purification, the substance is mixed with ethanol and the suspension heated to the boil, the greater part of the compound thereby dissolving. After cooling, the undissolved portion is filtered off with suction and the filtrate is gradually mixed with petroleum ether. Upon trituration, crystallisation commences. By means of the addition of a further amount of petroleum ether, precipitation of N_α-tosyl-4-aminocarbonylphenylalanine is completed: m.p. from 230°C. (decomp.); above 200°C. sublimation.

3.0 g of this alanine derivative are covered with 15 ml. thionyl chloride and the mixture is heated under reflux on a boiling water-bath for 60 minutes. Excess thionyl chloride is distilled off in a vacuum and the residue which remains behind is codistilled twice with anhydrous benzene.

2.5 g. of the acid chloride thus obtained are dissolved in anhydrous benzene and, with stirring, added dropwise to a solution of 1.2 g. piperidine in 10 ml. anhydrous benzene which has been cooled to 0 to 5°C. After the addition is complete, the reaction mixture is stirred at ambient temperature for a further hour. The suspension obtained is shaken up with 30 ml. 3N hydrochloric acid and the remaining crystal slurry is filtered off with suction, washed with a copious amount of water and dried. Purification is carried out by recrystallisation from ethanol to give N_α-tosyl-4-cyanophenylalanine piperidide; m.p. 221°C.

0.8 g. N_α-Tosyl-4-cyanophenylalanine piperidide are dissolved in pyridine which contains a few drops of triethylamine. Subsequently, a weak stream of hydrogen sulphide is passed through the solution for 4.5 hours. After standing for 24 hours at ambient temperature, the reaction mixture is stirred into a mixture of ice and hydrochloric acid, the thioamide thereby being obtained in solid form. It is filtered off with suction, washed with a copious amount of water and dried. For the further reaction,

recrystallisation of the thioamide thus obtained is not necessary; m.p. 224—227°C.; droplets from 220°C.

0.4 g. of this thioamide are dissolved, with warming, in acetone and shaken with 1.2 g. methyl iodide for 18 hours at ambient temperature in the absence of light. Th thiolmide acid ester hydroiodide is precipitated with petroleum ether and filtered off with suction.

0.4 g. of the thioimide acid ester hydroiodide is dissolved in anhydrous ethanol and the solution, after the addition of 0.06 g. ammonium acetate, heated for 2.5 hours at 70 to 80°C. Thereafter, it is filtered and substantially evaporated in a vacuum. The residue is taken up in a little anhydrous ethanol and N_α-tosyl-4-amidinophenylalanine piperidide hydroiodide precipitated out with petroleum ether. For purification, it is dissolved in methanol and reprecipitated with diethyl ether; m.p. 220—224°C.

Example 3

11.0 g. 4-Bromobenzaldehyde, 6.0 g. sodium cyanide and 24.0 g. ammonium carbonate are stirred in a mixture of 100 ml. ethanol and 100 ml. water for 1 hour at 60°C. Subsequently, the reaction mixture is heated under reflux for 5 minutes. After cooling, it is acidified with hydrochloric acid and again heated under reflux for 5 minutes. After cooling, the 5-(4-bromophenyl)-hydantoin formed is filtered off with suction and washed until neutral; m.p. 222—224°C.

10.0 g. of this compound are suspended in 100 ml, 60% sulphuric acid and heated under reflux until the compound dissolves. The hot solution is filtered and from it crystallises 4-bromophenylglycine hydrogen sulphate; m.p. 102—105°C.

12.0 g. of this amino acid salt are dissolved in 100 ml. 2N aqueous sodium hydroxide solution and the solution is shaken with a solution of 8.0 g. tosyl chloride in 75 ml. diethyl ether for 4 to 5 hours. The precipitate is filtered off with suction and worked up with 60 ml. 3N hydrochloric acid. The N-tosyl-4-bromophenylglycine formed is filtered off with suction, washed until neutral and recrystallized from aqueous methanol; m.p. 195—198°C.

4.0 g. of this compound are heated under reflux for 1 hour in 20 to 30 ml. anhydrous bezene with 8 ml. thionyl chloride. Subsequently, benzene and excess thionyl chloride are distilled off on a water-bath in a vacuum. The residue is codistilled twice with 30 ml. anhydrous benzene, then dissolved in 30 ml. anhydrous benzene and the benzene solution added dropwise, with ice cooling and stirring, to a mixture of 2.0 g. piperidine and 30 ml, anhydrous benzene. After stirring for 1 hour with ice cooling, N_α-tosyl-4-bromophenylglycine piperidine is filtered off with suction and recrystallised from aqueous ethanol; m.p. 162—164°C.

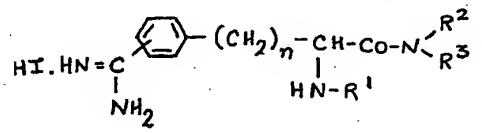
3.5 g. of this compound and 3.5 g. cuprous cyanide in 30 to 40 ml, dimethylformamide and 1 ml. pyridine are heated under reflux, while gassing with nitrogen. After 8 hours reaction periods, 3.5 g. cuprous cyanide are added thereto and heating continued. The hot solution is stirred into a mixture of ice and concentrated aqueous ammonia solution and the suspension stirred for 1 hour with 200 ml. chloroform. The chloroform phase is separated off and the aqueous phase shaken up several times with chloroform. The combined chloroform phases are successively washed with 3N hydrochloric acid and water and then dried over anhydrous sodium sulphate. The solvent is distilled off in a vacuum and the residue recrystallised from methanol to give N_α-tosyl-4-cyano-phenylglycine piperidide; m.p. 157—159°C.

2.5 g. of this cyano compound are dissolved in 15 ml. pyridine and a few drops of triethylamine and a stream of hydrogen sulphide is passed into the solution for 3 hours. After keeping for 12 hours at ambient temperature, the solution is poured on to a mixture of ice and hydrochloric acid. The precipitate is filtered off with suction, washed neutral with water and recrystallised from methanol to give the corresponding thioamide; m.p. 99—101°C.

1.0 g. of this thioamide is dissolved in acetone and mixed with 3.0 g. methyl iodide. After keeping for 2 days, with the exclusion of light, at ambient temperature, the thioamide acid ester salt is precipitated with diethyl ether or petroleum ether, filtered off with suction, washed with diethyl ether, dissolved in methanol and thereafter reprecipitated with diethyl ether to give the corresponding thioimide acid ester hydroiodide; m.p. 134—136°C.

0.8 g. of this thioimide acid ester hydroiodide and 0.12 g. ammonium acetate are dissolved in 20 ml. anhydrous methanol. The solution is kept for 3 hours at 60°C. and subsequently concentrated in a vacuum to one half of its volume. N_α-Tosyl-4-amidinophenylglycine piperidide hydroiodide is precipitated out with diethyl ether, dissolved in methanol and reprecipitated with diethyl ether; m.p. 162—165°C.

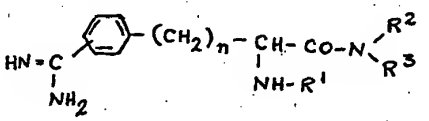
The following compounds are prepared in a manner analogous to that described above in Examples 2 and 3:



position of the amidino group	n	R^1	R^2	R^3	m.p. °C.
4	0	Tosyl			218—222
4	0	Tosyl			158—162
4	0	Naphthyl-2-sulphonyl			103—107
4	0	Naphthyl-2-sulphonyl			161—165
4	0	Naphthyl-2-sulphonyl			159—165
3	1	Tosyl			245—250
3	1	Tosyl			251—253
3	1	Tosyl			261—265
3	1	Tosyl	H	$(CH_2)_3—CH_3$	169—171
3	1	Naphthyl-2-sulphonyl			157—159
3	1	Naphthyl-2-sulphonyl			256—262
3	1	Naphthyl-2-sulphonyl			220—228
3	1	Naphthyl-2-sulphonyl	H	$(CH_2)_3—CH_3$	111—121
4	1	Tosyl			above 89 (decomp.)
4	1	Tosyl			above 95 (decomp.)
4	1	Tosyl	H	$(CH_2)_3—CH_3$	above 85 (decomp.)
4	1	Tosyl	H		133—143
4	1	Tosyl	H		above 108 (decomp.)
4	1	Naththyl-1-sulphonyl			above 142.5 (decomp.)
4	1	Naphthyl-1-sulphonyl			above 192 (decomp.)
4	1	Naphthyl-1-sulphonyl			above 84 (decomp.)
4	1	Naphthyl-1-sulphonyl	H	$(CH_2)_3—CH_3$	above 85.5 (decomp.)
4	1	Naphthyl-1-sulphonyl	H		148—155
4	1	Naphthyl-2-sulphonyl			above 236 (decomp.)
4	1	Naphthyl-2-sulphonyl			above 152 (decomp.)

Claims

1. Compounds of the general formula:—



wherein R^1 is an alkylsulphonyl radical containing up to 5 carbon atoms or an arylsulphonyl radical containing 6 to 10 carbon atoms, R^2 is a hydrogen atom, an alkyl radical containing up to 8 carbon atoms, an aryl radical containing 6 to 10 carbon atoms or an aralkyl radical containing up to 3 carbon atoms in the side chain, R^3 is an alkyl radical containing up to 8 carbon atoms, an aryl radical containing 6 to 10 carbon atoms or an aralkyl radical containing up to 3 carbon atoms in the side chain, or R^2 and R^3, together with the nitrogen atom to which they are attached, can also form a 5- to 7-membered heterocyclic ring which can contain one or more further heteroatoms and/or can be substituted and *n* is 0, 1, 2 or 3; as well as the acid-addition salts thereof with physiologically compatible inorganic and organic acids.

2. N_α-Tosyl-4-amidinophenylalanine piperidide hydrochloride.
3. N_α-Tosyl-4-amidinophenylalanine piperidide hydroiodide.
4. N_α-Tosyl-4-amidinophenylglycine piperidide hydroiodide.
5. N_α-Tosyl-4-amidinophenylglycine pyrrolidide hydroiodide.
6. N_α-Tosyl-4-amidinophenylglycine-morpholide hydroiodide.
7. N_α-(Naphthyl-2-sulphonyl)-4-amidinophenylglycinepyrrolidide hydroiodide.
8. N_α-(Naphthyl-2-sulphonyl)-4-amidinophenylglycinepiperidide hydroiodide.
9. N_α-(Naphthyl-2-sulphonyl)-4-amidinophenylglycinemorpholide hydroiodide.
10. N_α-Tosyl-3-amidinophenylalanine-piperidide hydroiodide.
11. N_α-Tosyl-3-amidinophenylalanine-pyrrolidide hydroiodide.
12. N_α-Tosyl-3-amidinophenylalanine-morpholide-hydroiodide.
13. N_α-Tosyl-3-amidinophenylalanine-*n*-butylamide hydroiodide.
14. N_α-(Naphthyl-2-sulphonyl)-3-amidinophenylalanine-piperidide hydroiodide.
15. N_α-(Naphthyl-2-sulphonyl)-3-amidinophenylalanine-pyrrolidide hydroiodide.
16. N_α-(Naphthyl-2-sulphonyl)3-amidinophenylalanine-morpholide hydroiodide.
17. N_α-(Naphthyl-2-sulphonyl)-3-amidinophenylalanine-*n*-butylamide hydroiodide.
18. N_α-Tosyl-4-amidinophenylalanine-pyrrolidide hydroiodide.
19. N_α-Tosyl-4-amidinophenylalanine-morpholide hydroiodide.
20. N_α-Tosyl-4-amidinophenylalanine-*n*-butylamide hydroiodide.
21. N_α-Tosyl-4-amidinophenylalanine-benzylamide hydroiodide.
22. N_α-Tosyl-4-amidinophenylalanine-α-naphthylamide hydroiodide.
23. N_α-(Naphthyl-1-sulphonyl)-4-amidinophenylalanine-piperidide hydroiodide.
24. N_α-(Naphthyl-1-sulphonyl)-4-amidinophenylalanine-pyrrolidide hydroiodide.
25. N_α-(Naphthyl-1-sulphonyl)-4-amidinophenylalanine-morpholide hydroiodide.
26. N_α-(Naphthyl-1-sulphonyl)-4-amidinophenylalanine-*n*-butylamide hydroiodide.
27. N_α-(Naphthyl-1-sulphonyl)-4-amidinophenylalanine-benzylamide hydroiodide.
28. N_α-(Naphthyl-2-sulphonyl)-4-amidinophenylalanine-piperidide hydroiodide.
29. N_α-(Naphthyl-2-sulphonyl)-4-amidinophenylalanine-pyrrolidide hydroiodide.

30. Process for the preparation of compounds of the general formula given in claim 1, wherein an appropriate halophenylalkyl halide is reacted with an appropriate acylaminomalonic acid ester to give an ω-(halophenyl)-alkylacylamino malonic acid diester which is converted into the corresponding ω-(halophenyl)-α-aminoalkylcarboxylic acid hydrochloride, acylation of which with an appropriate sulphonic acid chloride gives the corresponding N_α-alkylsulphonyl or N_α-arylsulphonyl compound, which is converted into the corresponding acid chloride, reaction of which with an appropriate amine gives the corresponding amide, whereafter the halogen substituent attached to the aromatic nucleus is replaced by a cyano group and this cyano compound reacted with a lower alcohol in the presence of an anhydrous hydrogen halide to give the desired compound in the form of a hydrohalide.

31. Process for the preparation of compounds of the general formula given in claim 1, wherein an appropriate cyanophenylalkyl halide is converted into an ω-(cyano-phenyl)-acylaminomalonic acid diester which is reacted at an elevated temperature with a mixture of glacial acetic acid and hydrochloric acid to give an ω-(carboxamidophenyl)-α-aminoalkyl-carboxylic acid hydrochloride and this is then acylated with an appropriate sulphonic acid chloride to give a corresponding N_α-alkylsulphonyl or N_α-arylsulphonyl compound which, after reaction with an excess of an inorganic acid chloride, by dehydration and acid chloride formation, gives a cyanophenyl compound with an acid chloride structure which is converted into an acid amide, this then reacted with a lower alcohol and a hydrogen halide to give an imide acid ester salt and this salt reacted with ammonia in alcoholic solution to give the desired product.

32. Process for the preparation of compounds of the general formula given in claim 1, wherein an ω-(cyano-phenyl)-N_α-alkylsulphonyl- or -N_α-arylsulphonyl-amino-alkylcarboxylic acid, prepared as in claim 30 or 31, is dissolved in triethylamine/pyridine and reacted with hydrogen sulphide to give the corresponding thiocarboxamido compound which is reacted with an alkyl halide to give the corresponding thioimide acid ester salt which, in turn, is reacted with ammonium acetate in ethanol to give the desired product.

33. Process for the preparation of compounds of the general formula given in claim 1, wherein a halophenylglycine is reacted with an appropriate sulphonylation compound to give the corresponding halophenyl-N_α-alkyl- or -N_α-arylsulphonylglycine which is converted via the acid chloride into the corresponding acid amide and this is reacted with cuprous cyanide in an organic solvent to give the corresponding cyanophenyl-N_α-alkyl- or -N_α-arylsulphonylglycinamide which is dissolved in triethylamine/pyridine and reacted with hydrogen sulphide to give a thiocarboxamido compound, reaction of which with an alkyl halide gives the corresponding thioimide acid ester salt which is reacted at an elevated temperature with ammonium acetate in ethanol to give the desired compound.

34. Process according to any of claims 30 to 33, wherein a salt obtained is converted into a different salt with a physiologically acceptable inorganic or organic acid.

35. Process according to any of claims 30 to 34, wherein a cyanobenzylacylaminomalonic acid diester is converted into the corresponding ω-(carboxamidophenyl)-α-aminoalkyl-carboxylic acid hydrochloride by reaction with equal parts of glacial acetic acid and 6N hydrochloric acid under reflux conditions.

36. Process according to any of claims 30 to 35, wherein a halogen atom attached to an aromatic nucleus is replaced by a cyano group by reaction with cuprous cyanide, the cuprous cyanide being added in several portions after reaction periods of 6 to 8 hours.

37. Process according to any of claims 30 to 36, whenever carried out in an inert gas atmosphere.

38. Process for the preparation of compounds according to claim 1, substantially as hereinbefore described and exemplified.

39. Compounds according to claim 1, whenever prepared by the process according to any of claims 30 to 38.

40. Pharmaceutical compositions, comprising at least one compound according to claim 1, in admixture with a solid or liquid pharmaceutical diluent or carrier.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1979. Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.